REMARKS

Brief Summary of the Present Invention

The present invention relates to a method for improving the efficacy of clinical drug trials. Specifically, the method of the present invention can be used to screen samples containing DNA from potential participants or participants to distinguish between participants who have Gilbert's Syndrome from participants experiencing an adverse reaction to the drug that is the subject of the clinical drug trial. Additionally, participants can be eliminated or included on the basis of whether such participants possess the genetic basis of Gilbert's Syndrome. Further, the present invention is of particular interest in regards to the interpretation of the results obtained from the clinical drug trial.

Brief Summary of the Office Action and Response

In the Office Action, claims 1-11 were rejected under 35 U.S.C. § 112(1) and 35 U.S.C. § 101. Additionally, the claims were rejected under 35 U.S.C. § 102 (b) and § 103 (a).

In the present Amendment, claim 1 has been cancelled, claims 2-13 have been amended, and claim 14 has been added. Thus, claims 2-14 are pending. The amendments to the existing claims and the newly added claim are fully supported in the specification and, thus, no new matter is added.

Rejections Under 35 U.S.C. § 112(2)

Claims 1-11 stand rejected under 35 U.S.C. 112, second paragraph. Claim 7 was specifically rejected under § 112 (2) as reciting "the DNA inner region" Claim 7 has been amended such that it no longer recites "the DNA inner region." Claim 7 now recites "a DNA region indicating the genetic basis for Gilbert's Syndrome..." Withdrawal of this rejection is requested. Claims 1-11 were rejected as not setting forth definite steps for the method or process of use. Claim 1 has been cancelled, rendering this rejection moot, and claims 2-11 have been amended to set forth specific steps in methods of the present invention. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 101

Similarly, claims 1-11 were rejected under §101 as not reciting statutory subject matter in that the recitation of a use without setting forth steps is improper. Claim 1 has been canceled and claims 2-11 have been amended such that they properly set forth the process of the present invention. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102(b)

Claim 12 was rejected under § 102(b) as anticipated by Bosma et al. Applicants respectfully traverse this rejection as applied to amended claim 12. Claim 12 is directed to a kit comprising primers and instructions directed

towards identifying clinical drug trial participants who have Gilbert's Syndrome. Bosma et al. does not disclose or suggest the use of primers in a kit for identifying clinical drug trial participants. Since there is no disclosure of instructions pertaining to the use of a kit, claim 12 is not anticipated by Bosma et al. Withdrawal of this rejection is requested.

Rejections Under 35 U.S.C. § 103 (a)

Claims 1-11 were rejected as unpatentable over Bosma et al. in view of Sibille et al. Applicants respectfully traverse this rejection. Claim 1 has been cancelled, rendering this rejection moot.

As acknowledged by the Examiner, Bosma et al teaches the genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's Syndrome. However, there is no indication whatsoever in Bosma et al that Gilbert's Syndrome may affect the outcome of clinical drug trials. In addition, the methods used to identify patients with Gilbert's Syndrome were not those typically used to determine those with Gilbert's Syndrome.

For example, to perform a correlation that is relevant and not affected by pre-analytical factors, individuals are required to abstain from alcohol and drugs for a period of 5 days prior to performing the analysis. The correlation demonstrated by Bosma et al is flawed because the population studied

did not undergo these restrictions. In fact, the lack of avoiding alcohol or drugs is likely to have resulted in some individuals with the genetic abnormality having 'normal' bilirubin levels and mistakenly determined as a control. Therefore, the skilled person would be cautious of using the teachings of this document. However, the data generated by the present inventor was obtained in a population that avoided alcohol and drugs for 5 days prior to analysis. This work was an improvement over that performed by Bosma et al.

Sibille et al teaches that healthy volunteers should be screened for subclinical illnesses in Phase I of clinical drug trials. Any subjects exhibiting subclinical illnesses are then removed from the drug trials. This document further suggests that those individuals with elevated bilirubin levels should be removed from the drug trial.

However, under normal conditions, the plasma bilirubin levels of many individuals with Gilbert's Syndrome are within the "normal" range defined in Sibille et al., that is, 4-26 μmol/l. It is only under fasting conditions that their levels of bilirubin become elevated. Therefore, many individuals with the syndrome would not be excluded from drug trials if one were to use the teaching of Sibille et al. Exclusion is, in fact, not necessarily desirable since up to 25% of some populations can have Gilbert's Syndrome and, therefore, this would exclude up to 25% of potential recipients for the drug under trial. Nevertheless, it is important to know if the participants have Gilbert's Syndrome in order that the results of the trial can be interpreted correctly. Thus, you may not wish to simply exclude such individuals as this would undesirably skew the results.

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Prior to the present invention, the techniques that were used to diagnose Gilbert's Syndrome were expensive and difficult to implement since all individuals involved in the drug trials had to avoid alcohol and medication for 5-7 days and fast for over 12 hours.

The present invention is simpler and less costly than the previous methods of identifying individuals with Gilbert's Syndrome since it negates the need for a pre-testing fast. In addition, the invention practically eliminates non-compliance by the test subjects.

Furthermore, since the invention does not choose to necessarily exclude individuals from the clinical drug trials but rather identifies them so as to allow the results to be adjusted accordingly, it does not exclude any significant part of a potential recipient population.

In view of the above, it is submitted that neither Bosma et al or Sibille et al suggest using an assay for screening individuals for Gilbert's Syndrome to improve the efficacy of drug trials. Therefore the claims presently on file are patentable over them.

Summary

In view of the foregoing amendments and remarks, the Applicant submit that this application is in condition for allowance and respectfully request early and favorable notification to that effect. If it would expedite prosecution of this application, the Examiner is invited to confer with the Applicant's undersigned attorney.

Respectfully submitted,

Allan Ratner, Reg. No. 19,717
Attorney for Applicant

PDP/lk
Enc - Version with markings to show changes made
Dated: December 20, 2001

Suite 301
One Westlakes, Berwyn
P.O. Box 980
Valley Forge, PA 19482-0980
(610) 407-0700

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

2. (Twice Amended) ~~Use of the test as claimed in claim 1 wherein~~ A method for screening individuals for participation in clinical drug trials, the method ~~comprise~~ comprising the steps of:

a) ~~taking~~ collecting a sample from ~~each participant or potential participant in a clinical drug trial~~ an individual,

b) screening the ~~samples~~ sample for ~~the~~ a genetic basis of Gilbert's Syndrome, and

c) ~~identifying such participants having~~ determining if the individual has the genetic basis of Gilbert's Syndrome, and

d) proceeding with the clinical drug trial based on the knowledge of such ~~participants~~ individuals possessing or not possessing the genetic basis of Gilbert's Syndrome.

3. (Three Times Amended) ~~Use of the test as claimed in claim 1~~ The method of claim 2 wherein the sample ~~is chosen from blood, buccal smear or any other sample containing~~ contains DNA from the ~~participants or potential participants~~ individual.

4. (Three Times Amended) ~~Use of the test as claimed in claim 1~~ The method of claim 2 wherein the method further comprises ~~the~~ a step:

~~of~~ eliminating ~~participants~~ individuals having the genetic basis of Gilbert's Syndrome from the clinical drug trial.

5. (Three Times Amended) ~~Use of the test as claimed in claim 1~~ The method of claim 2 wherein the method further comprises the step:

~~of~~ selecting ~~only participants~~ individuals having the genetic basis for Gilbert's Syndrome for the clinical drug trial.

6. (Three Times Amended) ~~Use of the test as claimed in claim 1~~ The method of claim 2 further comprising ~~the step of~~:

e) interpreting the results of the clinical drug trial ~~based on the knowledge that certain participants have~~ incorporating data regarding the genetic basis of Gilbert's Syndrome ~~as distinguished from participants adversely affected by the~~ in distinguishing adverse effects of a drug.

7. (Three Times Amended) ~~Use of the test as claimed in claim 1~~ The method of claim 2 wherein the method comprises the steps of:

a) isolating DNA from ~~each~~ the sample,

b) amplifying ~~the~~ a DNA ~~inner~~ region indicating the genetic basis for Gilbert's Syndrome to form DNA fragments,

c) isolating the amplified DNA fragments, and

d) identifying ~~participants~~ individuals having the genetic basis of Gilbert's Syndrome.

8. (Three Times Amended) ~~Use of the test as claimed in~~ The method of claim 7 wherein step b) the DNA is amplified using ~~the~~ a polymerase chain reaction (PCR) using a radioactively labeled pair of nucleotide primers.

9. (Three Times Amended) ~~Use of the test as claimed in~~ The method of claim 7 wherein the DNA region indicating the genetic basis of Gilbert's Syndrome is ~~the~~ a gene encoding UDP-glucuronosyltransferase (UGT).

10. (Three Times Amended) ~~Use of the test as claimed in~~ The method of claim 7 wherein the DNA to be amplified is in an upstream promoter region of the UGT 1*1 exon 1.

11. (Three Times Amended) ~~Use of the test as claimed in claims~~ The method of claim 7 wherein the DNA to be amplified includes ~~the regions~~ a region between -35 and -55 nucleotides at the 5' end of UGT 1*1 exon.

12. (Three Times Amended) A kit for screening participants ~~or potential participants in~~ for clinical drug trials, wherein the kit comprises primers for amplifying ~~DNA in the~~ a region of DNA ~~the genome~~ indicating ~~the~~ a genetic basis of Gilbert's Syndrome, and the kit further comprising instructions directing a user of the kit that the kit should be used to identify drug trial participants having the genetic basis for Gilbert's Syndrome.

13. (Three Times Amended) Primers for use ~~of the test as claimed in claim 1 including~~ in amplifying the DNA region in the method of claim 7, the primers comprising primer pairs, AB or CD as follows:

A/B: (A,5' - AAGTGAACTCCCTGCTACCTT-3' (SEQ ID NO:1),

B,5' -CCACTGGATCAACAGTATCT-3' (SEQ ID NO:2) or

C/D: (C,5' -GTCACGTGACACAGTCAAAC-3' (SEQ ID NO:3);

D 5' -TTTGCTCCTGCCAGAGGTT-3' (SEQ ID NO:4)).

Claim 1 has been cancelled.

Claim 14 has been added.